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Regional mortality differences in end-stage renal disease: How far can observational studies take us?

CP Kovesdy[1]

The survival of patients with ESRD living in various geographic regions is strikingly different. Efforts to determine the reasons behind this observation have been hampered by difficulties in adjusting for many characteristics that are inherently different in patient populations living on different continents. The mortality rate for the general population in a given region could be used to adjust for risk factors that would be otherwise difficult to quantify.

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Geographical differences in the mortality rate of patients with end-stage renal disease (ESRD) have been described for more than a decade. In a study by Held *et al.*,[1] the risk of mortality for patients on dialysis in the United States was 15% higher than the risk in Europe and 33% higher than that in Japan. The nephrology community received this observation with great interest, as it held the promise of identifying modifiable factors associated with mortality in ESRD. There is great variability in ESRD practice patterns across different continents, even though randomized controlled trials underlying these patterns are scarce. It thus seemed plausible to speculate that the different ways we treat our patients might be at least in part responsible for the discrepant mortality rates observed. In order to identify modifiable factors responsible for mortality, one would have to account for all the non-modifiable differences between the studied patient populations, a difficult task when patients are from different continents. This was clearly a challenge in the study by Held *et al.*,[1] as their data were obtained from different reporting systems and contained few variables to characterize the patient populations studied. The Dialysis Outcomes and Practice Patterns Study (DOPPS) offered the ideal remedy for this problem, as it uniformly recorded patient outcomes from dialysis units in Europe, Japan, and the United States, and it was also able to describe the characteristics of the different patient populations in extensive detail.[2] Not unexpectedly, it became clear that all ESRD patients are not equal: racial composition in various geographical areas is obviously different, and patients in the United States are older and have a higher burden of comorbidities.[3] Detailed adjustment for this heterogeneity alleviated somewhat the transcontinental mortality gap, but the difference remained significant nevertheless, again suggesting that variability in individual patient characteristics alone is not sufficient to explain the observed geographical diversity.[3]

Another seemingly plausible, yet very difficult-to-quantify, factor impacting on regional death-rate differences is the effect on mortality imparted by the sum of all the geographical, environmental, cultural, and socioeconomic effects that are unique to any given area. Differences in genetics, income level, diet and lifestyle, crime rate, access to health care, or air quality could all be important, yet it seems impossible to adjust for all these (and probably many more) individual factors when comparing the risk of mortality in patients from areas far from each other. Van Dijk *et al.*[4] (this issue) offer a simple and elegant solution to this problem: they used general population mortality rates as surrogate adjustment for a host of difficult-to-measure factors, assuming that all or most of these factors have a similar impact on people living in the same area, including patients with ESRD. The authors compared mortality rates in patients with ESRD and in the general population across a north–south divide in Europe and showed that general population mortality difference accounted for 26% of the regional

[1]*Department of Renal Medicine, Salem Veterans Affairs Medical Center, Salem, Virginia, USA and Department of Medicine, University of Virginia, Charlottesville, VA, USA.*
Correspondence: *CP Kovesdy, Department of Renal Medicine, Salem Veterans Affairs Medical Center, 1970 Roanoke Blvd., Salem, Virginia 24153, USA. E-mail: csaba.kovesdy@va.gov*

mortality difference in ESRD. Detailed patient characteristics were not available in the study by van Dijk *et al.*;[4] hence it is unclear what caused the remaining difference. The idea of using contrasting general population mortality rates as a backdrop when comparing ESRD mortality in different countries was briefly explored in the original study by Held *et al.*;[1] in an addendum to their article, the authors compared the differences in general population mortality with those recorded in the ESRD population in Japan, Europe, and the United States. General population mortality was lower in Japan than in the United States, but the difference was smaller than that recorded between the ESRD populations in the two countries, suggesting that some, but not all, of the difference in the ESRD population mortality might be attributable to factors specific to the studied geographic locations. Interestingly, though, the general population mortality in the United States was found to be lower than that in Europe, thus magnifying rather than alleviating the differences noted between ESRD mortality rates in these two regions.[1] A more detailed analysis of this kind was used by Wong *et al.*,[5] who compared ESRD mortality in Asian Americans versus other races in the United States and showed that race-specific general population death rates explained more than half of the variation in mortality imparted by race. In this latter study, patients of different races were not segregated in different geographic locations (as in studies comparing patients from different countries); hence the range of factors for which general population mortality might account was narrowed down to race-specific genetic, cultural, and/or socioeconomic diversity. This study also suggested that the differences in ESRD mortality rate between Japan and the United States may not be due to practice-related factors, as Asian-American patients with ESRD had a mortality rate similar to that of their counterparts in Japan.

These studies suggest that general population mortality rate could be used in future studies examining outcome discrepancies in different ESRD populations, along with detailed adjustments for individual patient characteristics. Some questions remain, though. It is unclear how valid such an approach would be in comparing large entities (such as mortality in Europe versus Japan versus the United States), given the clearly significant regional variations in both ESRD and general population mortality rates within these entities.[3–5] It is also unclear how the logic of using general population mortality to alleviate the differences in ESRD mortality across continents would apply in the case of the United States, where ESRD mortality is highest (when compared with those of Japan and Europe) and yet general population mortality is lower than that reported in Europe.[1]

At the end of the day we are still left with the question: what is the benefit of comparing ESRD populations from different regions? Practice patterns are being monitored in the DOPPS in order to identify factors associated with survival and other outcomes. The study by van Dijk *et al.*[4] has brought renewed attention to a tool that could enhance similar studies. But we must not forget that no matter how sophisticated our statistical methods are, the results of observational studies are mostly hypothesis-generating and cannot serve as ultimate proof of causality. They are at the same time indispensable to provide ideas that are worth exploring in randomized controlled trials.

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Weighing in on fistula failure

BS Dixon[1]

Obesity, though not commonly reported as a cause of fistula failure, may influence fistula survival by making it difficult to cannulate the vein and possibly by releasing adipokines, such as interleukin-6, tumor necrosis factor-α, plasminogen activator inhibitor-1, or adiponectin, that modulate the development of neointimal hyperplasia and thrombosis leading to fistula failure.

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Once established, an autogenous arteriovenous fistula has the lowest failure rate and fewest complications of any vascular access used for hemodialysis. The mortality rate and annual cost are also lower for patients with an arteriovenous fistula compared with patients undergoing hemodialysis using an arteriovenous graft or central venous catheter. No randomized trial comparing different modes of vascular access has been done to exclude the possible confounding effect of selection bias. Nonetheless, it is likely that the chronic inflammatory effects and infection risk of grafts and catheters account for much of the difference in complications, costs, and survival. Encouragingly, through the efforts of the Fistula First

[1]*Veterans Affairs Medical Center and University of Iowa School of Medicine, Iowa City, Iowa, USA*
Correspondence: *BS Dixon, Nephrology Division, University of Iowa School of Medicine, E300D GH, 200 Hawkins Drive, Iowa City, Iowa 52242-1081, USA. E-mail: bradley-dixon@uiowa.edu*